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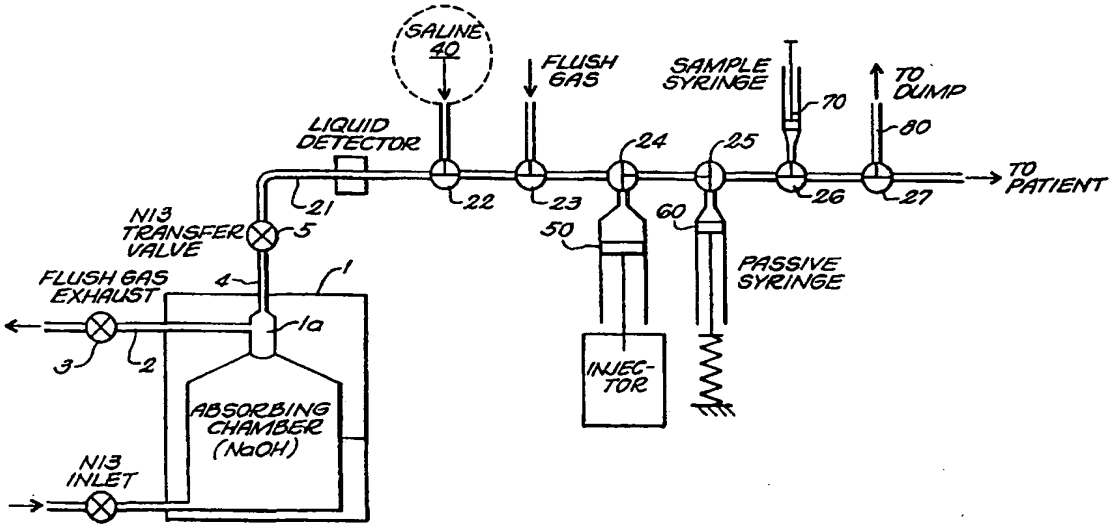

(57) Abstract

A radioactive material such as an unstable isotopic gas is provided to a receiving chamber (1) directly from a source to form a purified or enriched bubble. The bubble is passed to a fluid handling set for preparation of the reagent or other delivery system. In an exemplary embodiment trace amounts of nitrogen–13 are concentrated in a receiving chamber and passed into a small bubble of carrier gas. The carrier gas is then delivered into a fluid handling set. The fluid handling set connects to a pressure syringe (50) and a passive syringe (60), and further includes a plurality of flushable valves (22–27) interconnected as a closed unit by tubing (21) to form a switchable or finite state flow network in which the pressure syringe may back flush the tubing, mix the isotope in a delivery liquid, and transfer the mixed liquid to an output for diagnostic imaging or other use.

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RADIATION HANDLING SYSTEM AND SET

CROSS-REFERENCE TO RELATED APPLICATIONS

Not Applicable.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

Not Applicable.

BACKGROUND OF THE INVENTION

The present invention relates to the preparation and use of radioactive isotopes for biological purposes such as labeling, marking, imaging and diagnostics. Such applications generally utilize a single element containing minor amounts of an unstable isotope, which must be generally formed into a simple compound that is incorporated into a solution or reagent which undergoes a known or predictable interaction with the biological system being studied. Thus, for example, radionuclides are often added as labels to a substance that binds to a nucleic acid to indicate the presence of a particular substrate, termination or functional group. Similarly, materials which are taken up by particular biological systems may be labeled for treatment or imaging purposes. Aerosols or radio-labeled fluids may also be used for blood flow or lung function diagnostic imaging studies.

In general, it is necessary that radioactive materials be handled in such a way as to not expose the operator to radiation. Thus they are preferably handled under robotic control or automated conditions. It is desirable that the radioisotopes involved have a short half life, so as to automatically limit the exposure of the subject to radiation, and to facilitate proper disposal. However, materials with a short half life cannot be compounded in advance or stored for lengthy times. Such radionuclides must therefore be manufactured at or near to the site of intended use. In these cases the purification and preparation of the radionuclide in a suitable delivery system must also be accomplished locally. The brevity of the nuclide half life may further complicate its handling and processing. These factors have sometimes prevented the acceptance or use of otherwise worthwhile radionuclide-based procedures.

It would therefore be desirable to provide a convenient system for preparing radionuclides for biological use.

It would also be desirable to provide such a system for handling a radionuclide in an automated fashion without exposing the operator to radiation.

It would further be desirable to provide such a system useful for short-lived materials or small batches to enable the routine use of such materials in individual procedures.

SUMMARY OF THE INVENTION

These and other desirable features are achieved in a system in accordance with the present invention by providing a radioactive marker material such as an unstable isotopic gas to a receiving chamber directly from a source to undergo initial cleansing or concentration, and passing the material into a fluid handling set for automated preparation of the reagent or actual delivery system. In an exemplary embodiment, trace amounts of ^{13}N, created by proton bombardment of a target at a cyclotron, pass to a receiving chamber, are cleansed and pass into a small bubble of carrier gas. The carrier gas is then delivered into a fluid handling set. The fluid handling set includes or connects to a pressure syringe and a passive syringe, and further includes a plurality of flushable valves interconnected by tubing in a closed unit to form a flow network in which the pressure syringe may back-flush the tubing, mix the isotope in a delivery liquid, and transfer the mixed liquid to an output for diagnostic imaging or other use. The fluid handling set, which is a closed and preferably sterile unit, may include the receiving chamber 1, and it mounts in a fixed console of operating motors and condition sensors to control the various steps of fluid handling and delivery, and to effect safety functions which enable the system to connect directly to a catheter or to a vascular injection system for use on human beings.

In a preferred embodiment, the receiving chamber 1 is substantially rigid, but has a region of limited or unidirectional compliance. The chamber receives a flow of trace

isotope in a bulk gas, operating to remove the bulk gas while the radionuclide accumulates in a bubble at the outlet port of the chamber. Compliance of the receiving chamber may be effected by means of an elastic wall tensioned against a rigid support such that the wall flexes outwardly under pressure to accommodate the inflow of carrier gas but may not bow inwardly. This maintains the chamber volume above a fixed minimum, and prevents liquid from leaving the chamber when suction is applied at the top. In an illustrative system, nitrogen-13 is generated by cyclotron bombardment of a target with accelerated particles, and when the target has attained a sufficient level of radioactivity, the sample is passed to the receiving chamber and the CO_2 with trace ^{13}NN is bubbled into a sodium hydroxide solution. The one-way compliant wall allows a large flow to be received and maintained under pressure to accommodate the different rates of carrier delivery and carrier removal effected at this stage. The CO_2 reacts with and is effectively taken up by the sodium hydroxide solution, while the desired nuclide concentrates at a gas-filled plenum at the top of the receiving chamber, where it is accessed at the outlet port using a closed sterile set to effect transfer, mixing and delivery in a form useful for medical imaging. The fluid handling set includes a plurality of three way valves or medical infusion stopcocks that are preconnected together via small bore tubing to form a flow path. Two of the stopcocks each have a third port, which are attached to syringe bodies. One operates as an active bidirectional pump, while various motors and sensors in the console operate and control the position of the stopcock handles to achieve transfer, mixing and delivery of the radionuclide.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be more fully understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

Figure 1 is a flow chart illustrating major steps of the preparation process of the present system:

Figure 1A illustrates the system showing representative components in use for positron emission tomography;

Figure 2 illustrates system architecture as applied to a nitrogen 13 radionuclide;

Figure 3 illustrates a preferred construction of a receiving chamber for the system of Figure 2;

Figures 4A through 4D illustrate details of valve operation and flow for transfer of the radionuclide into a fluid handling set of the present invention;

Figure 5 illustrates an operating console for the set of the invention;

Figures 5A-5C illustrate stopcock mounting and control blocks of the console for use with a closed sterile set; and

Figure 6 illustrates another embodiment of the system and set.

DETAILED DESCRIPTION OF THE DRAWINGS

In accordance with a principal aspect of the present invention, there is provided a system for automated and isolated handling of a hazardous material, such as a radionuclide, for biological or medical use. The system includes a sterile set defining the path of the nuclide from a source or process chamber to its end use which, in the illustrated embodiment, involves injection into a patient. Other potential end uses may include specialized labeling, microanalytic or synthesis applications. As shown in Figure 1 for a representative system, the radionuclide, which in this case is nitrogen-13, passes from a source to a conditioning or purification chamber 1 which produces a small mass or bubble of the concentrated radionuclide for delivery to the preparation portion 10 of the system. The preparation portion 10 dissolves the nuclide in

a saline solution for injection in a patient, and may directly inject the prepared solution into the patient.

By way of technical background for this embodiment, the use of nitrogen-13 in gaseous form for medical imaging procedures was pioneered at the Hammersmith Hospital, in London, several decades ago. The radionuclide is produced by bombardment in a cyclotron using a number of possible target systems and sweep gases. Further details may be found in the text Short-lived Radioactive Gases for Clinical Use of J. C. Clark and P. D. Buckingham (Butterworth, London and Boston) pp 190-200. That text is hereby incorporated herein by reference. Nitrogen-13 is only very slightly soluble in blood, and when injected in solution in the blood stream, quickly leaves the blood and accumulates at the blood-air exchange interface in the lung. Its decay creates positrons which may provide excellent three dimensional PET images of the lung, for evaluation of both perfusion and ventilation. However, the difficulties of using this radionuclide have effectively prevented its adoption in hospital settings. Much of the discussion below is applicable to other gaseous radionuclides such as oxygen-15, or radionuclides incorporated in a gaseous medium, or in a liquid with appropriate modifications. However, the preparation and use of nitrogen-13 presents a number of technical difficulties and will therefore be discussed more fully to illustrate aspects of a system and components of the present invention.

In accordance with a principal aspect of the present invention the source radionuclide is provided in a relatively crude or bulk form, for example in a sweep gas or target fluid from a cyclotron, or in other primitive or intermediate form, and flows through the system to directly enter the patient or be applied to some other sterile or purified application such as marking, analysis or synthesis of a pure product. As shown in Figure 1A it is generally contemplated that the system 20 will be a small cabinet, desktop or other stand-alone unit containing the sub-assemblies 1, 10 (Figure 1), and which attaches to the source and to the patient either directly or via a small intermediate assembly. For example, the unit 20 may connect to the source through a filtration unit or the like, and to the patient via an infusion line, port or pressurized timed injector or the

like. However, most preferably the connection to the source and to the patient are as direct as possible so that little dead space, wasted volume, delay time or regions of radiation exposure are interposed between the source and the patient.

As further shown in Figure 1A, the invention generally contemplates that the unit 20 will be controlled as to several parameters discussed below by a connection to a keyboard/processor assembly 21. Also the specific nitrogen-13 embodiment is used in conjunction with an imaging or detection assembly 25. The assembly 25 of Figure 1A is a detector array which encircles the patient and is configured for positron emission tomography, to simultaneously detect the pair of annihilation photons emitted in opposite directions by positron-electron annihilations as the radionuclide decays. The detector 25 provides its detection signals to a processor for construction of a three dimensional image of the distribution of the positron-emitting radionuclide. Other suitable detectors include single-sided detector arrays, or even photographic plate cameras which register and record the received annihilation photons on a plate of film. However, a positron emission tomography (PET) instrument is the preferred detection instrument for the illustrated process.

Figure 2 illustrates functional component of the units 1, 10 of Figure 1. As shown, the unit 1 for carrying out preliminary cleansing or refinement of the radionuclide in this case includes an absorbing chamber through which the nitrogen-13 bubbles to remove the CO_2 sweep or residual target gas as the material arrives from the cyclotron source. The absorbing chamber 1 is filled with sodium hydroxide solution and is shaped with an inverted funnel cap that channels unabsorbed gas upward to a plenum 1a at the top of the chamber. Plenum 1a connects on the one hand to an exhaust port 2 controlled by an exhaust valve 3 and, on the other hand, to an outlet port 4 controlled by transfer valve 5. The outlet port connects to the main process line 21 of the sub-assembly 10, which as noted above resides within the preparation console 20 (Figure 1A) forming an inlet thereof and extending therethrough to the patient or end use. As described further below, chamber 1 may also be located within the console 20.

As further shown in Figure 2, the functional flow control and handling units appearing in the preparation console 20 include in addition to the flow line 21 a plurality of sterile three-way valves or stopcocks 22,... 27 each of which has two of its three ports connected to the line 21, and its third port connected to an inlet, outlet or syringe. The distal end of line 21 forms the output path from console 20. Each of the stopcocks 22-27 may be identical, and advantageously the stopcocks together with tube 21 are connected together and initially provided as a closed and sterile unit packaged in a manner similar, for example, to a medical infusion set. Each stopcock thus has one "free" port which is connected to allow material to enter, leave, or be moved along line 21. These third ports are attached to a source of sterile saline fluid 40, an active injector syringe 50, a source of flush fluid, and a passive holding syringe 60. In addition, a sample syringe 70 connects at stopcock 26, and an outlet line 80 to a dump, or waste vessel, extends from stopcock 27. These elements may also be connected as part of the set, although, as will be understood from the discussion below, variations are possible. The function of the sample syringe may be implemented instead by providing a small plenum with a pierceable septum connected to the third port of stopcock 26, and the line 80 may simply terminate with a spike port for attaching to a suitable collection vessel or transfer mechanism.

As further illustrated in Figure 2, the passive syringe is spring loaded so that it is normally biased to a non-extended, closed or minimal volume configuration. Thus, when a pressurized flow appears along line 21 and is directed into the syringe 60 by stopcock 25, its piston moves outwardly to form an adaptive chamber that changes volume under pressure for receiving the fluid in the line 21.

In accordance with a principal aspect of the present invention, the sterile set 21 includes a set of connected stopcocks and a syringe 50 all configured to fit within the control console (described further below) and to be manipulated by servomotor elements therein to carry out the radionuclide preparation and delivery to the patient. In a representative preparation and delivery protocol, the stopcocks are set to positions such that one or more stopcocks block the inlet, outlet or intermediate portion of the set, while

one or more stopcocks are open to interconnect various portions of the path for receiving, preparing or delivering the radionuclide. In particular, the set 21 defines a finite state flow path formed of sterile single use disposable elements that fit within a console adapted to secure and control both sets of elements. Advantageously, the console 20 may be configured as a cabinet having separate compartments and which may, for example, be hinged to open for inserting and changing the set. In the prototype, the receiving chamber 1 is housed in the back half with its outlet line 4 (Figure 1A) connecting through the middle wall of the cabinet so that the fluid line 21 (Figure 2), runs through an array of stopcock or syringe receiving recesses and control elements laid out along a path in the front half of the cabinet.

In this embodiment, the apparatus is conveniently divided into those parts that do not contact the sterile solution, and those parts which do. The parts which contact the saline directly are sterile, and are assembled from disposable medical components. These include all of the tubing downstream of the liquid detector, the stopcocks, and the three syringes 50, 60, 70 which are disposable, and are to be replaced for each patient. These components are mounted on the front panel of the main unit, so that they can be changed quickly. The remaining parts of the system do not contact the saline, and may advantageously be made of reusable components. Thus the absorbing chamber 1, and the various solenoid valves and tubing that connect to it may be permanently installed. Preferably, the system is enclosed in a cabinet which is connected to a high flow-rate vacuum to maintain a steady flow into the cabinet through its small openings, so that any leaks of radioactivity within the system are contained and the radioactive material is removed.

The cabinet is divided into three compartments. The rear compartment, accessible via a rear door, contains the absorbing chamber and a dump tank. This compartment is watertight so that a catastrophic failure of the absorbing chamber will not result in escape of sodium hydroxide. A central compartment houses all of the electronics of the apparatus, and is protected from contact with any liquid that may leak from a failing component or connection. The front of the cabinet forms a door which

encloses the front panel, allowing easy access to components of the system that need to be changed frequently. Preferably the syringes mount on this panel.

Figure 3 shows a preferred construction for the receiving chamber 1, which may be formed of a strong medical grade polymer. As shown, the receiving vessel 1 is configured with a rigid housing 101 which may for example be formed of a hard plastic and having an interior with a major lower portion configured with a sloped roof leading to a chimney-like upper portion or outlet plenum 109 of defined volume. The vessel 101 is configured to fit on a magnetic base such as a stand having an internally mounted rotating permanent magnet driver mechanism positioned below the chamber support surface, and a magnetic stirring rod 107 is positioned in the bottom of the vessel 1. The main chamber communicates through a passage 102 to a secondary chamber 101a bounded by a flexible elastic membrane or wall 104 positioned over the passage 102. This serves as a compliant chamber; the membrane 104 bends outwardly as pressure increases in the chamber 1 and fluid flows through the passage into the secondary chamber. However, housing 101 is rigid and the passage 102 is relatively small, or else may consist of a number of small passages such that the wall below the flexible sheet 104 forms a perforated plate that supports the sheet and effectively prevents the sheet 104 from moving inwardly in response to negative pressure. This arrangement provides a stable volume within chamber 1, and accommodates a large influx of fluid so that when radioactive material from the cyclotron enters the inlet, a large bolus of material may be received, increasing the pressure and allowing the material to more effectively react in the absorbing chamber at the slower process rate of absorption therein. As discussed briefly above for the illustrated CO_2/nitrogen-13 material, chamber 1 is filled with a sodium hydroxide solution and is gently stirred by a magnetic stirring rod, so the solution quickly reacts with and effectively removes all the CO_2 while the unreactive nitrogen tracer rises into the outlet plenum 109 at the top of the chamber.

Preferably, for this process, the plenum 109 is initially loaded with a small volume, e.g. a few cubic centimeters, of a carrier gas in which the nitrogen-13 is soluble. This carrier may, for example, be nitrous oxide or other suitable biocompatible

gas. It is also advantageous that the carrier be highly soluble in blood or aqueous solutions, so that as discussed further below, problems of bubble formation or potential danger of bends are avoided. Thus, operation of the receiving chamber 1 is such that the sweep gas or target predecessor material from the source is removed, and the cleansed or concentrated radionuclide resides in the plenum 109 with a carrier gas for transfer through the transfer valve to the flow path 21. The architecture of vessel 1 therefore retains the pocket of gas at the top of the chamber intact. In this way, no liquid infiltrates the tubing leading to the rest of the apparatus, where small droplets of liquid might cause false triggering of the liquid detector or blocking of the hydrophobic filter.

An important aspect of the design of the compliant compartment is that it is only compliant to positive volumes. That is, volume can be added to the chamber, but not withdrawn. Once the carbon dioxide is absorbed, and the bubble of nitrogen withdrawn, the membrane wall lies flat against the side wall of the chamber, and the chamber becomes rigid. Thus it is impossible to suck significant volumes of sodium hydroxide out of the absorbing chamber and into the rest of the system.

Skipping ahead to Figure 5, there is shown a representative front panel of the console assembly 20 with the radionuclide entry port and elements of the flow path 21 laid out thereon. As shown, the flow line 21 first passes through a liquid detector which detects the arrival of liquid in the flow line from the chamber 1 and provides a control signal used, as described further below, for switching the states of the various stopcocks and transporting the bubble of radionuclide through the processing stages of the preparation assembly 10.

As further shown in Figure 5 a hydrophobic filter 29b is placed in the flow line 21 as a barrier to entry of liquid from chamber 1 into the system 10. As shown, the fluid preparation line 21 or set, is positioned in the console 20 such that each of the stopcocks 22-27 fits within a corresponding receiving block 22a through 27a, and the injection syringe 50 and passive syringe 60 fit within a driver mounting 50a and a syringe support 60a, respectively. By way of example, the driver assembly for the injector syringe may be that of, or similar to, a manual or programmed contrast agent injector system capable

of operation to drive a standard disposable syringe at high pressures through one or more precisely timed and controlled displacements to inject preset doses or volumes into the vascular system of a patient. The mounting 60a for the passive syringe may include a spring-loaded or counter-weighted platform or pushing member against which the distal end of the plunger of the injection syringe rides, so that the biased member returns the piston to its upper position (as shown) when the state of the stopcocks allows flow and the pressure in line 21 drops below the spring bias threshold.

In the prototype embodiment, the injector drive consisted of a MedRad radiographic contrast injection instrument, and the remainder of the cabinet and control mechanism of unit 20 was built atop the injector mount so that the active syringe was conveniently located in immediate proximity to the other elements shown in Figure 2. The stopcock mounting assemblies were prepared as shown in Figures 5A through 5C, by constructing shaped plastic receiving blocks having recesses each shaped to accept a standard disposable stopcock assembly therein and to mount on a plate so that each stopcock engages a position reporting actuator mechanism, which turns the handle of the stopcock. The stopcock was placed into the housing with the handle facing forward and the housing was designed to grip the three fluid connecting stubs of the stopcock, thus securely holding the stopcock body in a fixed position that allowed stopcock position to be controlled to within about one degree. A molded coupling was used to connect the stopcock handle to a standard servomotor, which in turn was controlled by a microcontroller board connected via a serial line to a computer used to control the apparatus. The computer was programmed to control operation of the stopcocks to define different segments for receiving, transferring, mixing and delivering the material. It was also programmed to control the injection regimen of the syringe for delivery of prepared doses to the patient.

In the prototype embodiment, the servomotor assemblies were modified so that the output of an internal potentiometer was passed to an A/D converter on the microcontroller board, and this output was used to calibrate the stopcock positions and then continuously monitor the position of each stopcock. Control software in the

microprocessor with a graphical user interface allowed the user to set the position of the stopcock and displayed the position on the screen, signaling an alarm if a motor fails to drive a stopcock element to the programmed position. For preparing the nitrogen-13 tracer, the program was written to effect a sequence of control steps as described below, and delivery steps were controlled by using the injector both to control the preparation of the solution and the injection into the patient.

Figure 4 illustrates a particular sequence for transfer of the tracer bubble from the absorbing chamber 1 into the mixing syringe, which is performed by encapsulating the tracer bubble with a saline solution. In broad terms, the operating sequence proceeded as follows. Before gas is received from the cyclotron the system is readied for production. The tubing from the absorbing chamber is flushed with a gas and the remainder of the apparatus is flushed and filled with de-gassed saline solution. One suitable flush gas is nitrous oxide but many other gases may be used. The chief requirements are that the gas be biologically safe, soluble in water and be non-reactive with the reagents used (sodium hydroxide, in this case). The radioactive gas is then admitted to the absorbing chamber and is stirred with a magnetic stirrer until all carbon dioxide is absorbed. Stirring is performed gently to avoid generation of droplets which might clog the hydrophobic filter 29b (Figure 5). The bubble of remaining gas at the top of the absorbing chamber is then transferred to the injector syringe which is otherwise filled with an appropriate amount of de-gassed saline for the contemplated infusion regiment or for the amount or available radionuclide. The mixture in the injector is next dissolved by repeatedly ejecting it into the passive syringe allowing its return and again ejecting it, so that by the vigorous flow and atomizing action of ejection the tracer is quickly dissolved in the saline solution. This process of vigorous atomization mixing by repeated passage through a flow segment between syringes in a closed set thus effectively addresses the difficult problem of preparing the radionuclide solution in a manner that is both safe and quick.

Next, with the stopcocks reset to define a different flow segment, a sample of the injectate so prepared is expelled from the syringe into the sampling syringe 80. Preferably a pH sensor is also present in the apparatus downstream of the injector

syringe to detect any sodium hydroxide contamination which may have occurred, and to actuate a shutdown in that event. The strength of the prepared solution is determined and this data is entered in suitable program for the injection control or image processing. The stopcock configurations are again changed, and the injector then gives a rapid bolus of tracer solution along its output line into the patient.

Returning now to Figure 4, there is shown a representative sequence of states of the finite state flow segment operating sequence of the device, illustrating in this case the initial radionuclide transfer from the receiving chamber 1 into the preparation set 10. After the initial system preparation and cleansing in chamber 1 are completed, the state of the apparatus is as depicted in Figure 4A. The upstream tubing (on the left) of stopcock 22 is filled with flush gas and the downstream tubing (to the right) is filled with degassed saline. The syringe 50 is then operated to draw along line 21 so that, as shown in Figure 4B the bubble of radioactive gas is drawn out of the pocket 109 (Figure 3), and toward the injector syringe 50. Sodium hydroxide solution is also drawn out of the absorbing chamber 1 at the trailing edge of the bubble of carrier/tracer gas. A liquid detector 29a is installed in the assembly 10 about the line 21 just upstream of the first stopcock 22 to provide a signal when the sodium hydroxide reaches this point. The transfer valve (Figure 3) is then closed, and the controller moves the first stopcock (Figure 4C) to connect the saline reservoir and fill in behind the bubble with saline solution from the reservoir. The bubble of tracer is thus "encapsulated" by saline solution as shown in Figure 4D. This allows controlled transfer through the apparatus by operation of the injector syringe. A slight amount of tracer gas still residing in the first stopcock and liquid detector is wasted. However, it will be understood that all tubing interconnecting the various components in the processing section 10 is of small size (under one millimeter), of the type customarily used for transfer of small volumes of fluid, and thus the wasted tracer represents a very small proportion of the carrier/tracer bubble being processed.

After the bubble of gas is completely drawn into the injector syringe, the stopcocks are moved to define a new flow/transfer segment such that the injector outlet

communicates only with the adjacent passive syringe. The mixture is then vigorously expelled into the passive syringe, then again drawn back into the active syringe and re-expelled. This process of repeated ejection promotes dissolution of the gas in several ways. Firstly, the surface area of the interface is increased exponentially by atomizing the fluid and in subsequent ejections breaking bubbles of gas into many smaller bubbles. Secondly, the ejection occurs at elevated pressure, thus enhancing the mechanisms of diffusion. Finally, the strong current and highly turbulent flow during ejection mixes the liquid very well, reducing any concentration gradients that might otherwise limit the process.

After the mixing process is complete, the stopcocks are again repositioned and the syringe 50 is operated to expel to the dump a volume equal to the volume of gas originally drawn into the syringe. This assures that any undissolved gas is ejected from the system. The lines to the patient are then flushed with the prepared tracer solution, and a small (1 ml) sample is taken. For the illustrated system, the sample is used primarily to assess the activity of the solution, but it could be additionally analyzed to check the composition of the injectate, or when applied to other radionuclide systems could determine other relevant conditions or parameters.

The pH of the solution is preferably measured by a sensor installed on the line to the dump tank. Any sodium hydroxide contamination is detected at this point, before injection to a patient.

In the foregoing system, it is important that the solution injected into the patient not be super-saturated and not contain any gas bubbles. If the solution were super-saturated, there would be a risk that bubbles could spontaneously appear in the solution before infusion or that microbubbles of nitrogen would form in the bloodstream causing an artificially-induced form of decompression sickness ('the bends'). To assure that supersaturation does not occur, the volume of nitrogen withdrawn from the absorbing chamber is limited to that volume which is known to dissolve in the volume of saline being prepared, and following dissolution, the mixture is allowed to equilibrate at atmospheric pressure. Thus, even if the solution is super-saturated, excess gas will

diffuse out of the solution. Further, when, following the mixing described above, the volume at least as great as the volume of gas originally drawn in from the absorbing chamber is ejected from the top of the injector syringe to dump, both the excess undissolved gas and the gas that has come out of solution are expelled.

Preferably, an ultrasonic bubble detector is also installed on the line to the patient, as well as a bubble-trap filter. Prior to injection, the lines are flushed, and a final, visual check for microbubbles is performed.

Figure 6 illustrates another embodiment of the system and set of the present invention. In this embodiment, the compliance chamber or flexible-walled side chamber may be actively pressed. This may be done to assure complete return of the flexible wall, and thus further guard against expulsion of the sodium hydroxide solution. Furthermore, the stopcocks are located somewhat differently to provide a short direct infusion path to the patient, and to separate or shift other paths or path segments. As in the first embodiment, the pressure syringe is centrally located, and serves as a hub for drawing, expelling or moving fluid along the various segment defined by the states of the stopcock valves. Advantageously, the pressure syringe mounts vertically, so that it initially receives and segregates the gas, and subsequently expels residual bubbles to the dump.

For operation of the system, the saline may be drawn from a USP-standard infusion bag, and all parts of the apparatus that contact the solution are assembled using aseptic technique from sterile, disposable medical components. Microporous filters are installed on the line entering the system from the saline bag, and on the line out of the system to the patient. Preferably a batch of tracer solution is prepared before the batch intended for infusion, and a sample is assayed.

Preferably, the bolus infusion of tracer is given by the injector under computer control, with the computer programmed to accurately control the infusate volume and rate, to effectively synchronize with a PET camera, and to automatically adjust dosage as the tracer decays. However, preferably the hardware is designed so that if necessary, the injector can be disconnected and operated manually. In the prototype embodiment using

an existing, manually-operated contrast media injector, the addition of a microprocessor-based controller and other modifications made to the injector were such that all of its safety-features function normally, and when manually-operated, the injector was fundamentally the same device as an unmodified, FDA-approved original. The series architecture of the treatment vessel and mixing assembly, together with the unique bubble transfer mechanism and multiple redundant stops and operation safety checks thus forms a system that is safely interposed between a cyclotron target and the patient's vasculature. Repetitive ejection between syringes produces a highly effective mixing/solution mechanism using fungible disposables. Moreover, the provision of a closed, disposable set for handling and compounding the radionuclide in an automated negative pressure safety cabinet allows the operator to maintain a safe distance from radiation, and provides a convenient system for the remote handling and preparation of diverse medicines, reagents and tracer materials.

The invention has been described above in a particular application for receiving, preparing and injecting a gaseous radionuclide for pulmonary PET imaging. However, the unique remote handling, sterile mixing, and volumetric control achieved by the set and the operating console are applicable with slight changes to compounding and delivering medications, marking and synthesizing materials and other radiation-handling tasks. Thus, it should be understood that the invention is not to be limited by the particular embodiments shown and discussed above, but may take other forms and be embodied in diverse systems for preparing, reacting, formulating or delivering radionuclides or biologically active materials. The invention and its principals of operation being thus disclosed, one skilled in the art will appreciate further features and advantages of the invention, and will be lead to further variations and modifications of the invention. Accordingly, all such variations and modifications are considered to be within the spirit and scope of applicant's invention as defined by claims appended hereto and equivalents thereof. All publications and references cited herein are expressly incorporated herein by reference in their entirety.

Claims

1. A system for preparation and delivery of a biologically active, hazardous or radioactive fluid, the system comprising

a receiving system having a first port for receiving said fluid and a second port positioned for delivering said fluid

a fluid handling set including a syringe and a plurality of flushable valves interconnected as a closed unit by tubing extending to an outlet

the syringe connecting via said fluid handling set to said second port and to said outlet for drawing the fluid into the tubing and transferring said fluid to the outlet as a prepared liquid

and the fluid handling set being configured for operation of said valves to define a finite set of flow segments at different times in said set such that the syringe flushes, fills, prepares and delivers the prepared fluid without exposing the operator to radiation.

2. A system for preparation and delivery of a biologically active, hazardous or radioactive material such as a gas, the system comprising

a receiving chamber having a first port for receiving said fluid and a second port positioned for accessing an active gas present in said material

an operating assembly for mounting a fluid handling set including a pressure syringe, a passive syringe and a plurality of flushable valves interconnected as a closed unit by tubing such that the tubing connects to said second port, and the operating assembly being configured to secure and operate the pressure syringe and the plurality of valves in sequence such that the pressure syringe draws the material into the pressure syringe and transfers the material with liquid to said passive syringe so as to form a prepared liquid, and furtheroperating said valves to define a finite set of flow segments at different times in said set for flushing, filling, preparing and delivering the prepared liquid, to receive the material from a source and provide the prepared liquid to a patient.

3. A system for preparation and delivery of a biologically active, hazardous or radioactive material, the system comprising

a receiving chamber having a first port for receiving said material and a second port positioned for accumulating a desired portion of the material

a fluid handling set including a plurality of flushable valves interconnected as a closed unit by tubing and configured for automated remote operation of said valves to form a finite state flow path effective to receive and encapsulate said desired portion as a bubble, prepare said portion in a delivery liquid and transfer the delivery liquid to an output.

4. The system of claim 3, wherein said valves define flow segments at different times in said set for flushing, filling, preparing and delivering the material such that the set receives the material as a gas from a source and safely delivers the delivery liquid to the bloodstream of a patient.

5. The system of claim 4, wherein the fluid handling set includes a pressure syringe operable for drawing the material into the set, mixing the delivery liquid, and delivering the delivery liquid into the bloodstream of a patient.

6. The system of claim 3 or 4, wherein the system prepares a gaseous radionuclide for injection to perform positron emission tomographic images of the patient.

7. The system of claim 3, wherein the fluid handling set is sterile assembly and further comprises and active syringe connected to one of said valves, and a passive syringe connected to another of said valves for receiving liquid such that the set is operable to prepare said portion in said delivery liquid by ejecting said portion and delivery liquid from the active syringe into the passive syringe.

8. A system for sterile preparation of a fluid radionuclide for use, such system comprising a sterile flow set including an inlet, an outlet, a plurality of stopcocks arranged in a sequence along a flow line to define a plurality of fluid transport segments, and first

and second syringes connected to the flow line being operable to form a sterile liquid solution of said radionuclide while it remains in the flow set by repeated ejection from said first syringe to said second syringe and return to said first syringe.

9. A system according to claim 8, wherein the sterile flow set includes at least five stopcocks.

10. A system according to claim 8, wherein at least one of said syringes attaches directly to a port of one of the stopcocks.

11. A fluid handling set for use in receiving a hazardous fluid material and forming a delivery liquid, such set comprising a plurality of at least five stopcocks and tubing interconnecting said plurality of stopcocks to form a closed transport path for handling the hazardous fluid material, each stopcock further having a port for admitting material to or expelling material from said closed transport path.

12. A device for receiving a hazardous fluid material and forming a delivery liquid such as a reagent, medicine or imaging agent containing said fluid material, such device comprising

a plurality of stopcock receptacles arranged along a path,

a corresponding plurality of servomotors positioned and configured for individually controlling a stopcock each being positioned in one of the receptacles,

a syringe driver, and

a controller operative to control said servomotors to form a set of flow segments along a closed transport path for handling the hazardous fluid material, and to control said syringe driver to drive a syringe so that the syringe draws said fluid material into the transport path and moves the fluid material along ones of said flow segments so as to prepare and deliver the delivery fluid.

13. The device of claim 12, further comprising a flow set including a plurality of stopcocks interconnected by tubing to form a sterile flow path, an active syringe connected to said flow path, and a passive syringe connected to said flow path.

14. The device of claim 13, wherein the controller is operative to control said servomotors to define a path between the active syringe and the passive syringe, and to prepare the fluid material by repeated ejection of the material from the active syringe to the passive syringe.

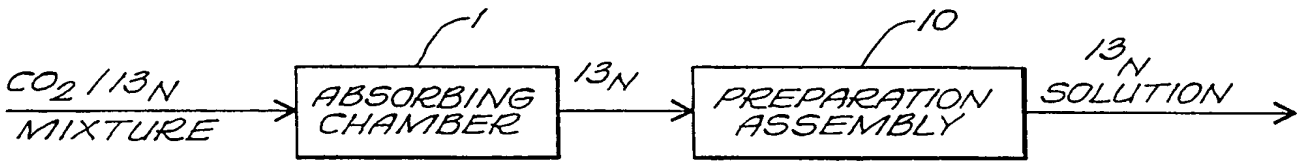
CO_2 / ^{13}N MIXTURE
1
ABSORBING CHAMBER
^{13}N
10
PREPARATION ASSEMBLY
^{13}N SOLUTION

FIG. 1

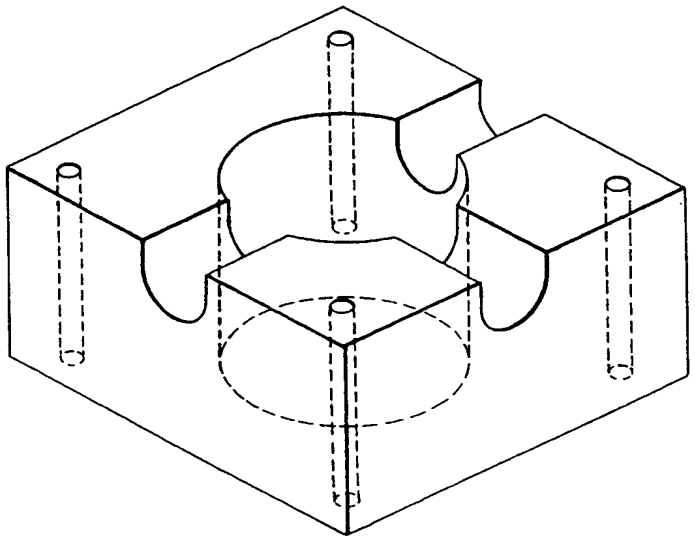

FIG. 5A

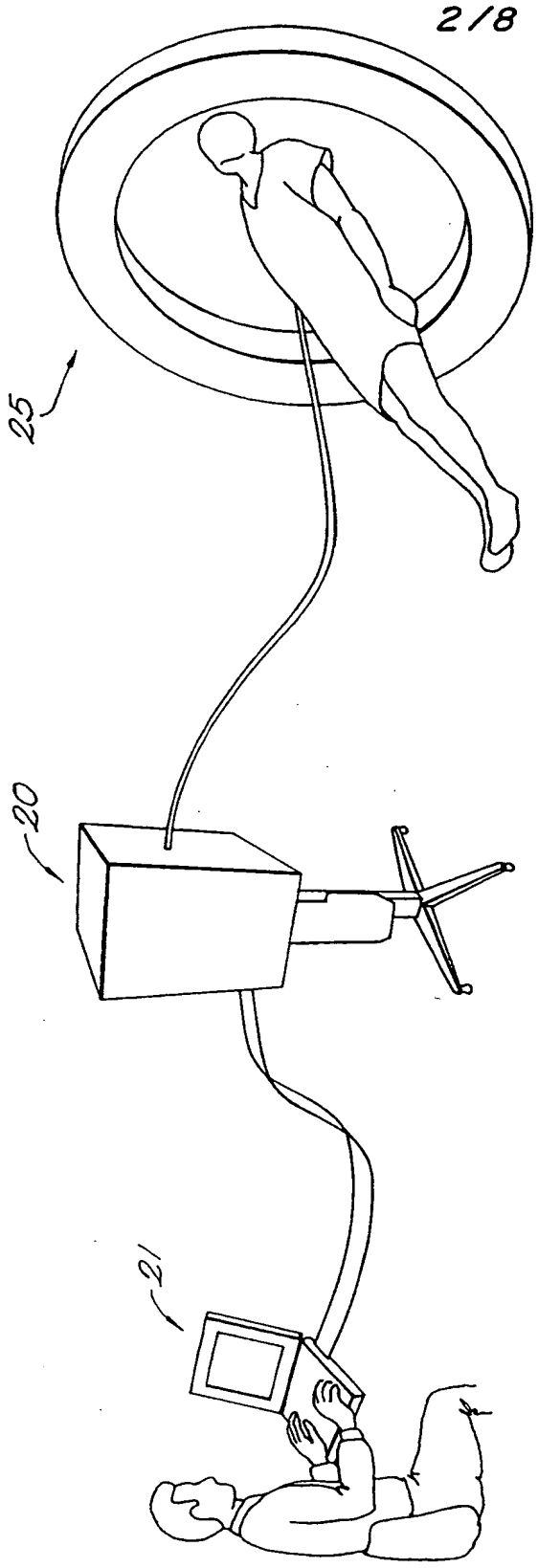

FIG. 1A

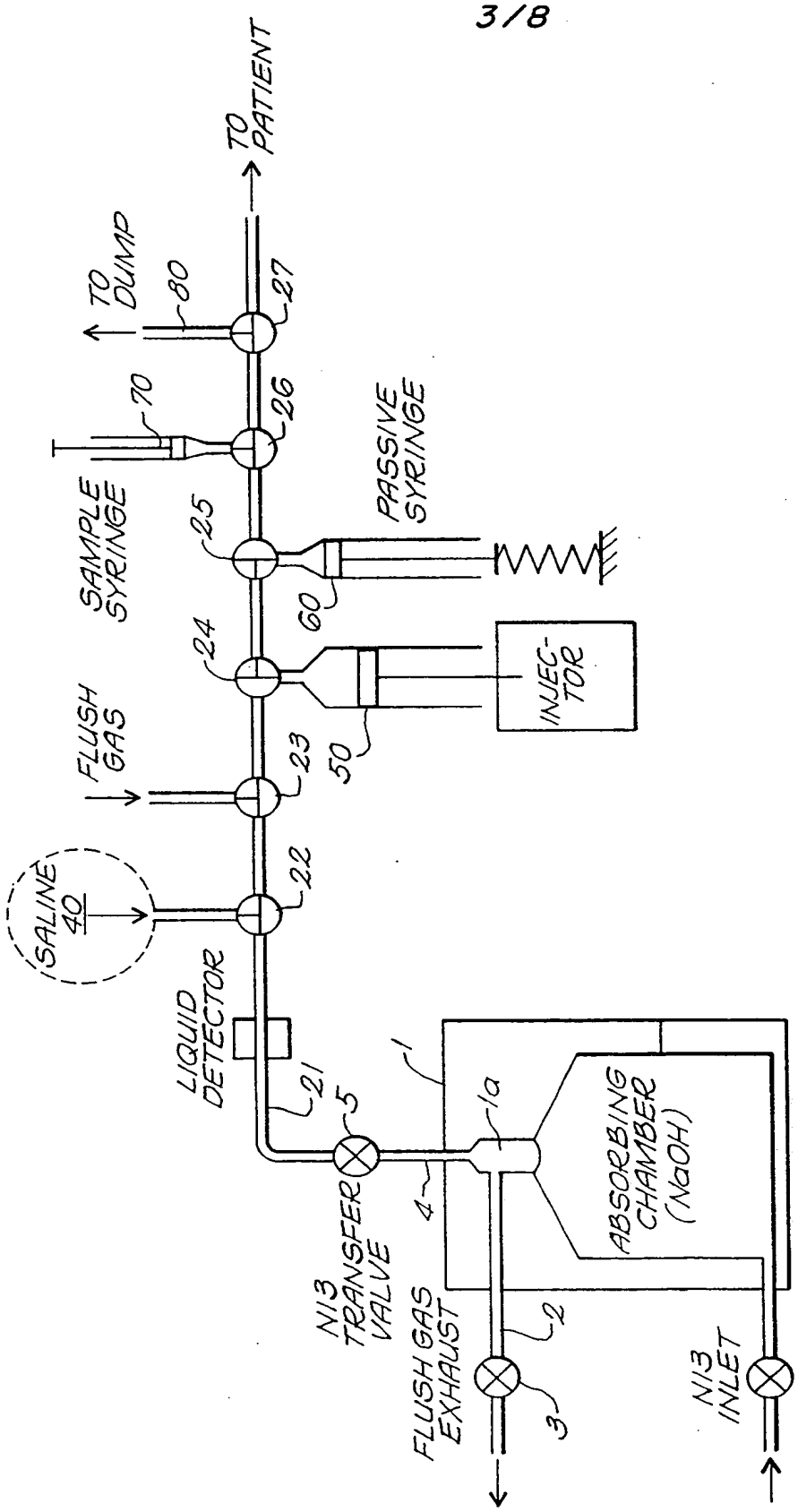
TO PATIENT
TO DUMP
80
27
70
26
PASSIVE SYRINGE
SAMPLE SYRINGE
25
60
24
INJEC-TOR
50
FLUSH GAS
23
SALINE 40
22
LIQUID DETECTOR
21
5
1
1a
ABSORBING CHAMBER (NaOH)
4
N13 TRANSFER VALVE
2
FLUSH GAS EXHAUST
3
N13 INLET

FIG. 2

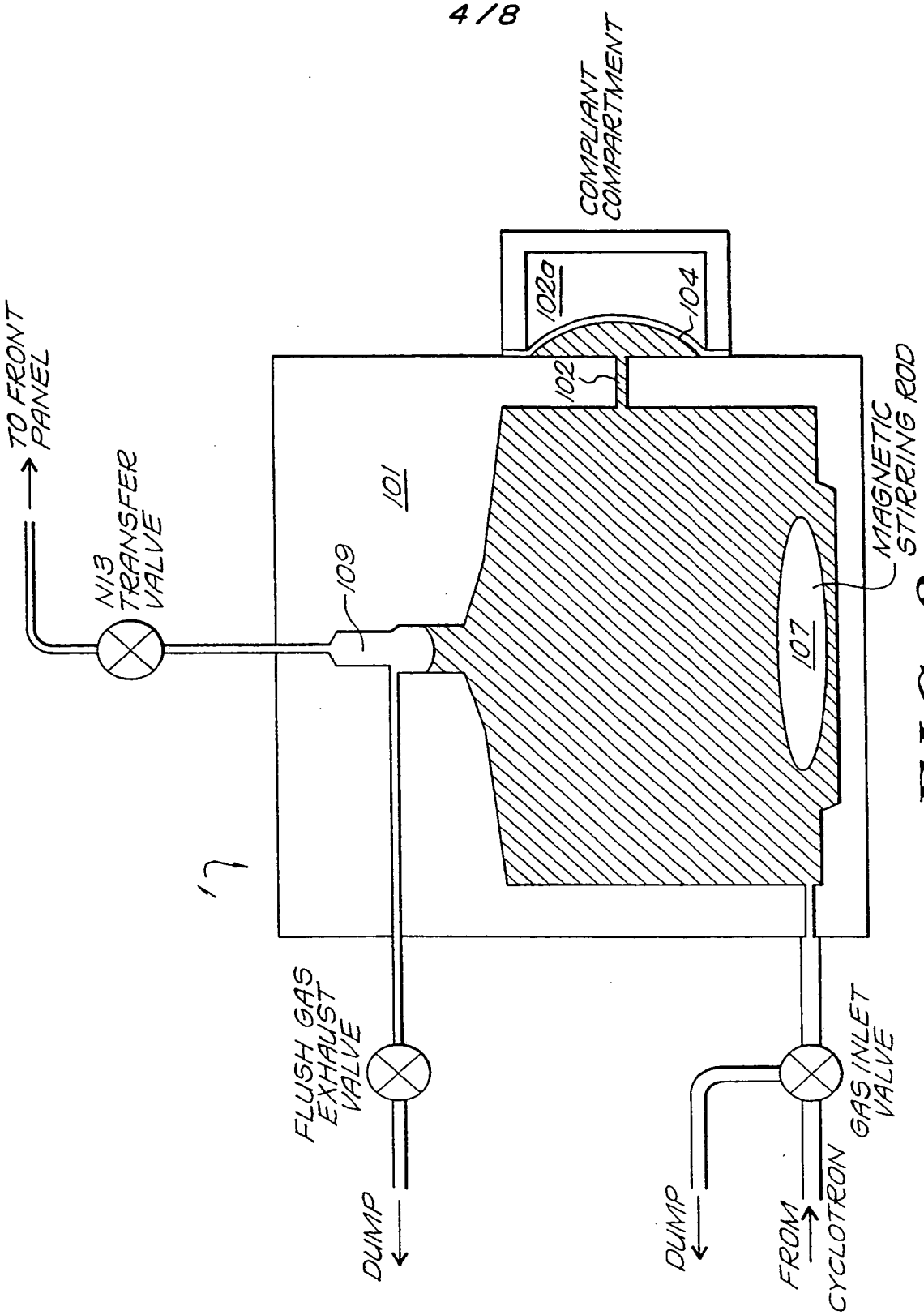
COMPLIANT COMPARTMENT
102a
104
102
101
TO FRONT PANEL
N13 TRANSFER VALVE
109
MAGNETIC STIRRING ROD
107
FLUSH GAS EXHAUST VALVE
DUMP
DUMP
FROM CYCLOTRON
GAS INLET VALVE

FIG. 3

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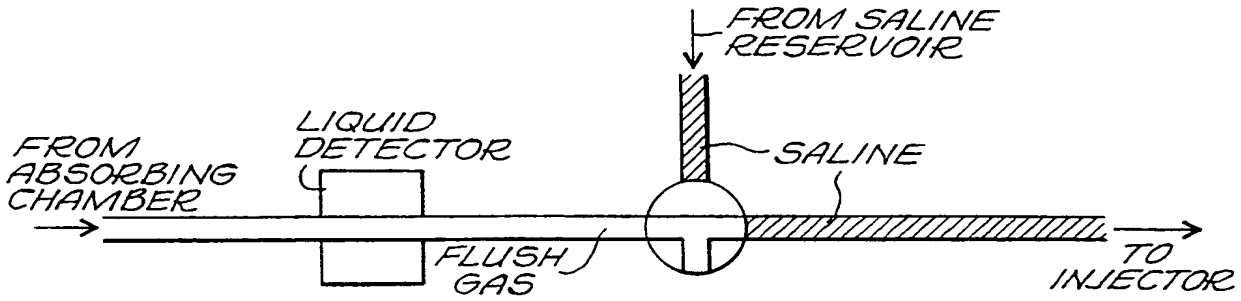

FIG. 4A

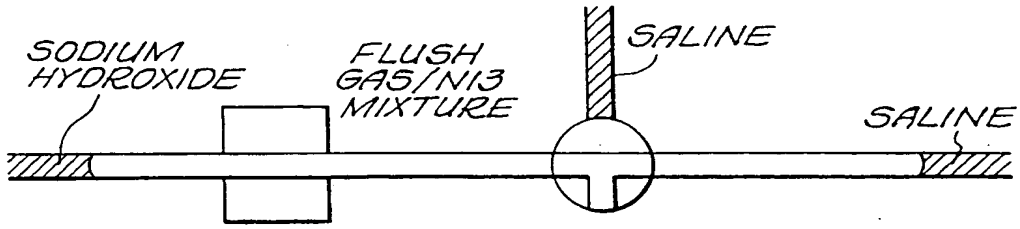

FIG. 4B

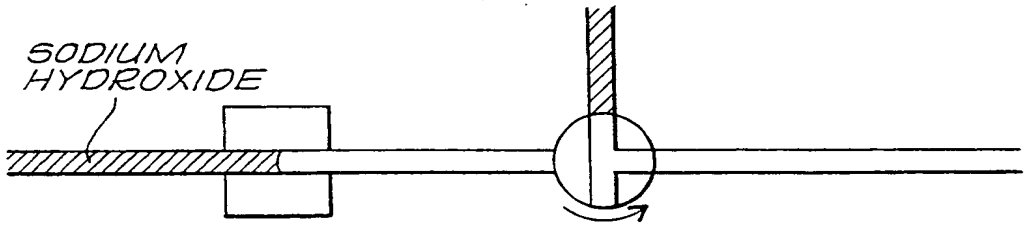

FIG. 4C

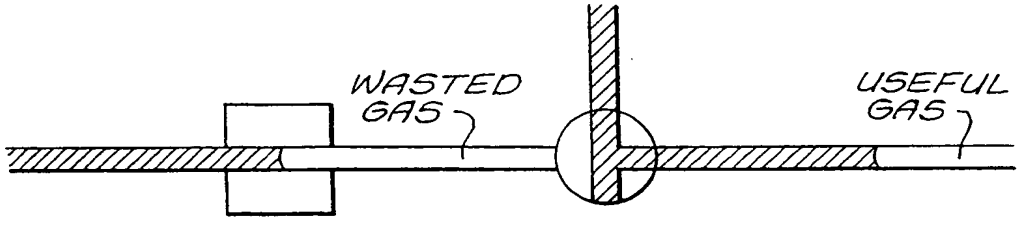

FIG. 4D

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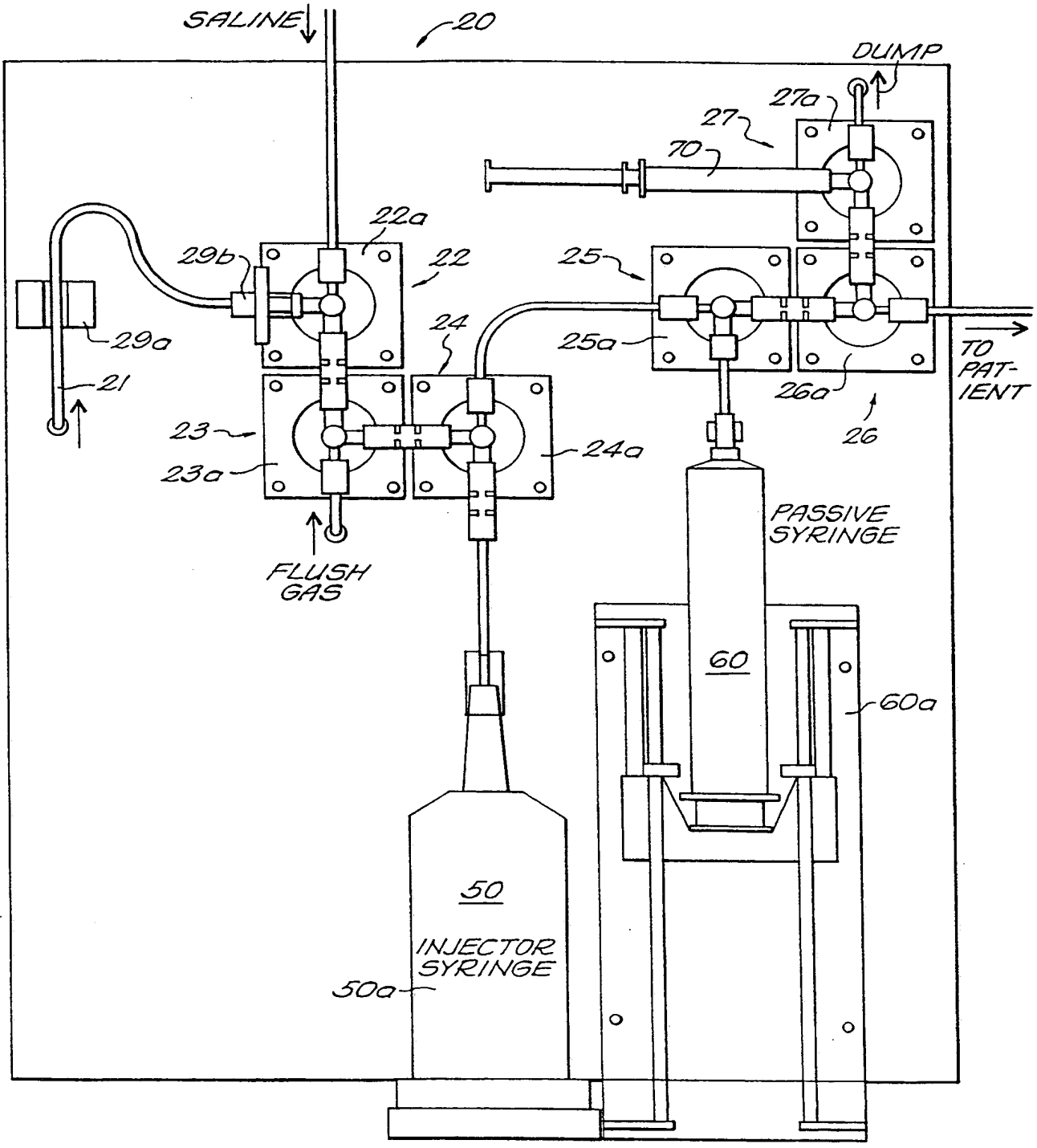
SALINE
20
DUMP
27a
27
70
22a
29b
22
25
24
25a
TO PAT-IENT
29a
21
26a
26
23
24a
23a
PASSIVE SYRINGE
FLUSH GAS
60
60a
50
INJECTOR SYRINGE
50a

FIG. 5

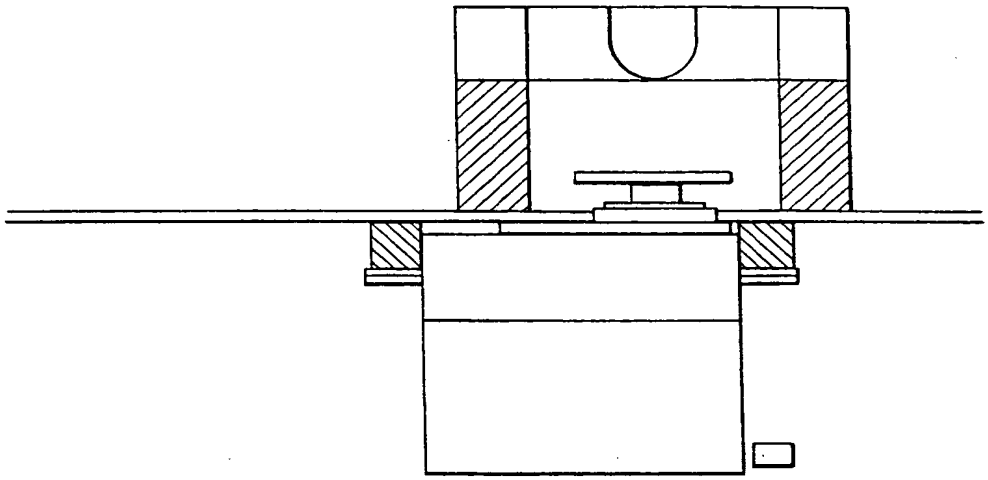

FIG. 5B

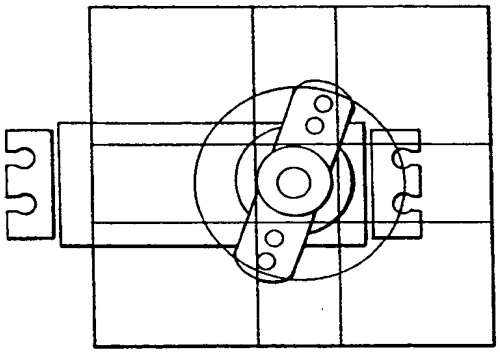

FIG. 5C

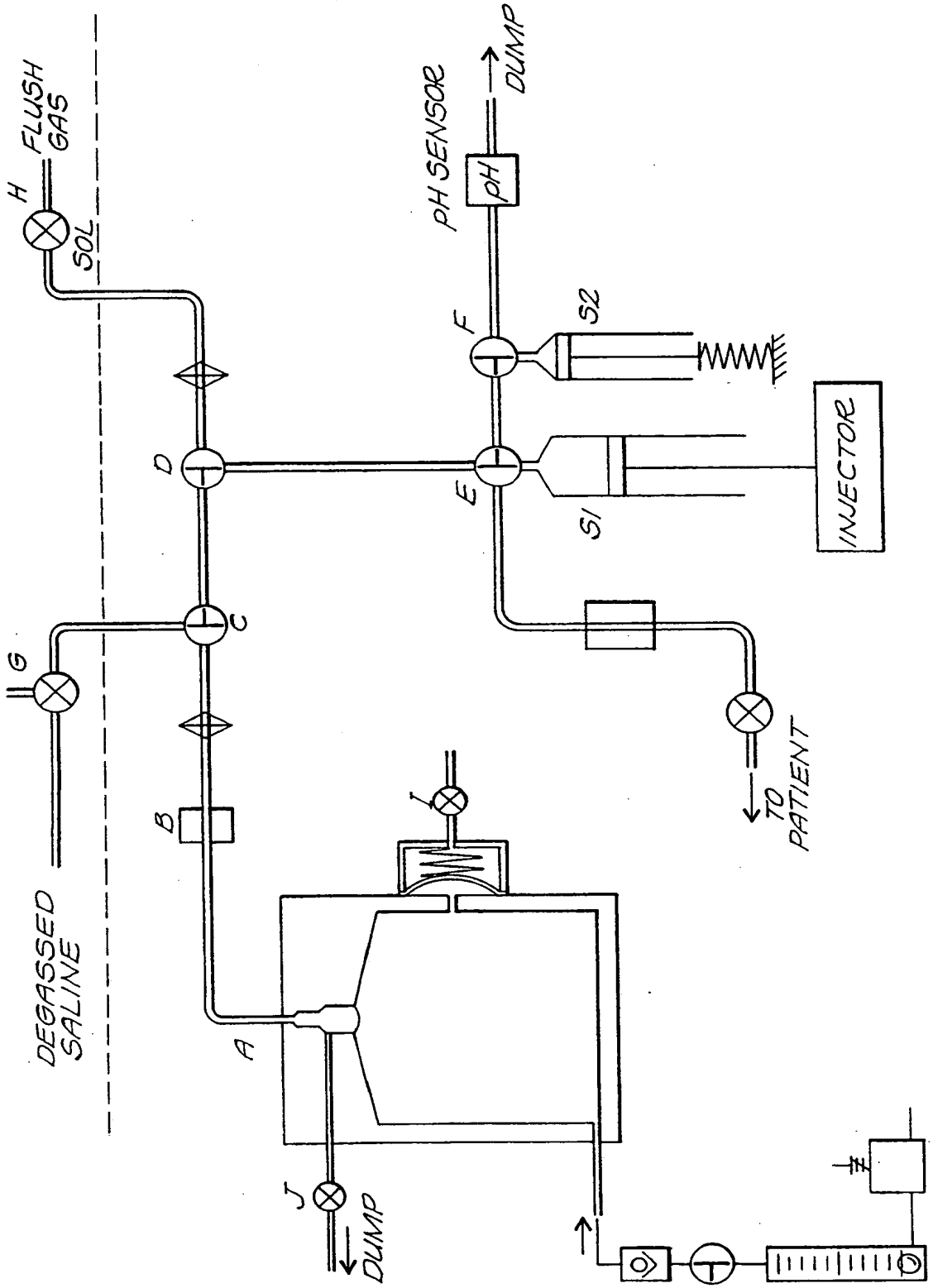
H
FLUSH GAS
SOL
pH SENSOR
pH
DUMP
F
S2
D
E
S1
INJECTOR
G
C
B
I
TO PATIENT
DEGASSED SALINE
A
J
DUMP

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/08981

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 24/00, 37/00
US CL :436/57, 174, 180; 422/81, 100, 903

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/57, 174, 180; 422/81, 100, 903

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,482,865 A (FERRIERI et al) 09 January 1996, entire document.	1-14
A	US 5,514,071 A (SIELAFF, JR. et al) 07 May 1996, entire document.	1-14
A	US 5,468,355 A (SHEFER et al) 21 November 1995, entire document.	1-14
A	US 5,223,434 A (KANNO et al) 29 June 1993, entire document.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 19 JULY 1999	Date of mailing of the international search report 19 AUG 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEFFREY R. SNAY Telephone No. (703) 308-0661

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 December 1999 (23.12.99)	
International application No. PCT/US99/08981	**Applicant's or agent's file reference** 22727-30
International filing date (day/month/year) 26 April 1999 (26.04.99)	**Priority date** (day/month/year) 27 April 1998 (27.04.98)
Applicant LAYFIELD, Dominick et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 November 1999 (17.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Kiwa Mpay
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

FALKOFF, Michael, I.
Nutter, McClennen & Fish, LLP
One International Place
Boston, MA 02110-2699
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 30 July 1999 (30.07.99)	
Applicant's or agent's file reference 22727-30	**IMPORTANT NOTIFICATION**
International application No. PCT/US99/08981	International filing date (day/month/year) 26 April 1999 (26.04.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 27 April 1998 (27.04.98)
Applicant THE GENERAL HOSPITAL CORPORATION et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
27 Apri 1998 (27.04.98)	60/083,133	US	10 July 1999 (10.07.99)

RECEIVED
AUG 0 9 1999
N.M.F.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Marc Salzman

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

FALKOFF, Michael, I.
Nutter, McClennen & Fish, LLP
One International Place
Boston, MA 02110-2699
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 23 December 1999 (23.12.99)	
Applicant's or agent's file reference 22727-30	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US99/08981	26 April 1999 (26.04.99)	27 April 1998 (27.04.98)

Applicant
THE GENERAL HOSPITAL CORPORATION et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :JP,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   None

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Kiwa Mpay

Telephone No. (41-22) 338.83.38

29/02

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

3

Applicant's or agent's file reference 22727-30	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/08981	International filing date *(day/month/year)* 26 APRIL 1999	Priority date *(day/month/year)* 27 APRIL 1998
International Patent Classification (IPC) or national classification and IPC IPC(6): G01N 24/00, 37/00 and US Cl.: 436/57, 174, 180; 422/81, 100, 903		
Applicant THE GENERAL HOSPITAL CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets.

   ☑ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17 NOVEMBER 1999	04 JANUARY 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JEFFREY R. SNAY DEBORAH THOMAS PARALEGAL SPECIALIST
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0661

Form PCT/IPEA/409 (cover sheet) (January 1994)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/08981

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages 1-16 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-14 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-8 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/08981

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-14	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-14	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-14	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-14 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the presently claimed combination of a receiving system and fluid handling system, including flushable valves, such that automated delivery of short-lived radionuclides in a closed system is enabled.

The claimed invention exhibits industrial applicability as a means for safe handling and delivery of short lived radionuclides in biological processes.

---------- NEW CITATIONS ----------

NONE

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MICHAEL I. FALKOFF
NUTTER, MCCLENNEN & FISH, LLP
ONE INTERNATIONAL PLACE
BOSTON MA 02110-2699

PCT

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*: 15 DEC 1999

Applicant's or agent's file reference: 22727-30

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/08981	26 APR 99	27 APR 98

Applicant: THE GENERAL HOSPITAL CORPORATION

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

   17 NOV 1999 (17.11.99)

2. That date of receipt is:

   ☑ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

   ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

   ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION**: That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

   ☐ *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/US
Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231 Attn: IPEA/US
Facsimile No.

Authorized officer
Tyetta Young
PCT/Internat'l Appl Processing Div
Telephone No. (703) 305-3671

Form PCT/IPEA/402 (July 1998)

RECEIVED
DEC 20 1999

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: MICHAEL I. FALKOFF
NUTTER, MCCLENNEN & FISH, LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2699

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	25 FEB 2000

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
22727-30	

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/08981	26 APRIL 1999	27 APRIL 1998

Applicant
THE GENERAL HOSPITAL CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	JEFFREY R. SNAY DEBORAH THOMAS PARALEGAL SPECIALIST
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0661

Form PCT/IPEA/416 (July 1992)★

The demand must be filed directly with the competent International Preliminary Examining Authority or one or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/US

CHAPTER II

PCT

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated.).

For International Preliminary Examination Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: **22727-30**

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US99/08981	**26 April 1999 (26.04.99)**	**27 April 1998 (27.04.98)**

Title of invention

RADIATION HANDLING SYSTEM AND SET

Box No. II APPLICANT(S)

Name and Address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

THE GENERAL HOSPITAL CORPORATION
55 Fruit Street
Boston, Massachusetts 02114
United States of America

Telephone No.:

Facsimile No.:

Teleprinter No.: **n/a**

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	**US**

Name and Address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LAYFIELD, Dominick
53 Park Street
Somerville, Massachusetts 02143
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	**US**

Name and Address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VENEGAS, José
12 Laurel Road
Swampscott, Massachusetts 01907
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	**US**

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US99/08981

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ **agent** ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointments of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FALKOFF, Michael I.
Nutter, McClennen & Fish, LLP
One International Place
Boston, Massachusetts 02110-2699
United States of America

Telephone No.
(617)439-2879

Facsimile No.
(617)973-9748

Teleprinter No.
n/a

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

☒ the international application as originally filed

the description	☒	as originally filed
	☐	as amended under Article 34
the claims	☒	as originally filed
	☐	as amended under Article 19 (together with accompanying statement)
	☐	as amended under Article 34
the drawings	☒	as originally filed
	☐	as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not year expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☒ **which is the language in which the international application was filed.**

☐ which is the language of a translation furnished for the purposes of international search.

☒ **which is the language of publication of the international application.**

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES: The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* excluding the following States which the applicant wishes not to elect:

International application No.
PCT/US99/08981

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international applicant	:	sheets		
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ **fee calculation sheet**
2. ☐ amendments under Article 34
3. ☐ copy of general power of attorney; reference number, if any
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and/or amino acid sequence listing in computer readable form
6. ☒ other (specify): **Transmittal Letter**

Box No. IX SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Michael I. Falkoff — **Dated:** 12.11.99

Dominick Layfield — **Dated:** 11/12/99 (12NOV99)

José Venegas — **Dated:** 11/12/99 (12 Nov. 99)

For International Preliminary Examination Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of the demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Date received from the IPEA on::

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

For International Preliminary Examination Authority use only

International application No: **PCT/US99/08981**

Date stamp of the IPEA

Applicant's or agent's file reference: **22727-30**

Applicant(s): **THE GENERAL HOSPITAL CORPORATION** et al

Calculation of prescribed fees

1. Preliminary examination fee	$490.00	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at* H is 25% of the handling fee.)	$162.00	H
3. Total of prescribed fees. Add the amounts entered at P and H and enter total in the TOTAL box	$652.00 TOTAL	

Mode of Payment

- ☐ authorization to charge deposit account with the IPEA (see below)
- ☒ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☐ other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available to all IPEAS)*

The IPEA/US
- ☐ is hereby authorized to charge the total fees indicated above to my deposit account
- ☒ *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account

141449	17.11.99	Michael I. Falkoff
Deposit Account Number	Date (day/mo/year)	

See Notes to the fee calculation sheet

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference: **22727-30**
(if desired) (12 characters maximum)

Box No. I TITLE OF INVENTION
RADIATION HANDLING SYSTEM AND SET

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

THE GENERAL HOSPITAL CORPORATION
55 Fruit Street
Boston, Massachusetts 02114
United States of America

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.
n/a

State *(i.e. country)* of nationality:
US

State *(i.e. country)* of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LAYFIELD, Dominick
53 Park Street
Somerville, Massachusetts 02143
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:
US

State *(i.e. country)* of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FALKOFF, Michael I.
Nutter, McClennen & Fish, LLP
One International Place
Boston, Massachusetts 02110-2699
United States of America

Telephone No.
(617) 439-2879

Facsimile No.
(617) 973-9748

Teleprinter No.
N/A

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VENEGAS, José
12 Laurel Road
Swampscott, Massachusetts 01907
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: **US**

State *(i.e. country)* of residence: **US**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

- ☐ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*.....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☐ **AL** Albania
- ☐ **AM** Armenia .....
- ☐ **AT** Austria .....
- ☐ **AU** Australia .....
- ☐ **AZ** Azerbaijan
- ☐ **BA** Bosnia and Herzegovina
- ☐ **BB** Barbados
- ☐ **BG** Bulgaria .....
- ☐ **BR** Brazil .....
- ☐ **BY** Belarus
- ☐ **CA** Canada
- ☐ **CH and LI** Switzerland and Liechtenstein
- ☐ **CN** China .....
- ☐ **CU** Cuba .....
- ☐ **CZ** Czech Republic .....
- ☐ **DE** Germany .....
- ☐ **DK** Denmark .....
- ☐ **EE** Estonia .....
- ☐ **ES** Spain .....
- ☐ **FI** Finland .....
- ☐ **GB** United Kingdom
- ☐ **GD** Grenada .....
- ☐ **GE** Georgia .....
- ☐ **GH** Ghana .....
- ☐ **GM** Gambia
- ☐ **HR** Croatia .....
- ☐ **HU** Hungary .....
- ☐ **ID** Indonesia
- ☐ **IL** Israel .....
- ☐ **IN** India .....
- ☐ **IS** Iceland
- ☒ **JP** Japan .....
- ☐ **KE** Kenya .....
- ☐ **KG** Kyrgyzstan .....
- ☐ **KP** Democratic People's Republic of Korea ..
- ☐ **KR** Republic of Korea .....
- ☐ **KZ** Kazakstan .....
- ☐ **LC** Saint Lucia .....
- ☐ **LK** Sri Lanka
- ☐ **LR** Liberia
- ☐ **LS** Lesotho .....
- ☐ **LT** Lithuania
- ☐ **LU** Luxembourg .....
- ☐ **LV** Latvia
- ☐ **MD** Republic of Moldova .....
- ☐ **MG** Madagascar .....
- ☐ **MK** The former Yugoslav Republic of Macedonia . .....
- ☐ **MN** Mongolia
- ☐ **MW** Malawi .....
- ☐ **MX** Mexico .....
- ☐ **NO** Norway
- ☐ **NZ** New Zealand .....
- ☐ **PL** Poland .....
- ☐ **PT** Portugal .....
- ☐ **RO** Romania
- ☐ **RU** Russian Federation .....
- ☐ **SD** Sudan
- ☐ **SE** Sweden
- ☐ **SG** Singapore
- ☐ **SI** Slovenia .....
- ☐ **SK** Slovakia .....
- ☐ **SL** Sierra Leone
- ☐ **TJ** Tajikistan .....
- ☐ **TM** Turkmenistan .....
- ☐ **TR** Turkey .....
- ☐ **TT** Trinidad and Tobago .....
- ☐ **UA** Ukraine .....
- ☐ **UG** Uganda .....
- ☒ **US** United States of America (see Cont. Box V)
- ☐ **UZ** Uzbekistan .....
- ☐ **VN** Viet Nam
- ☐ **YU** Yugoslavia
- ☐ **ZW** Zimbabwe.....

Check-boxes reserved for designating states (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

Continuation of Box IV

Agent:

GEARY, William C. III
ENGELLENNER, Thomas J.
DURKEE, Paul D.
ROSENBERG, Michelle B.
CAHILL, Ronald E.
DeLaCRUZ, Cedric G.
DeFRANCO, Carl M., Jr.
FALKOFF, Michael I.
ROTHENBERGER, Scott D.

The above attorneys and agents are members of the firm of Nutter, McClennen & Fish, LLP. Address, telephone number, facsimile number and teleprinter number of all are indicated in Box IV.

Continuation of Box V
In the US, priority of document (1) in Box VI is claimed under 35 USC §119(e)

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

	Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: National Application: Country	Regional Application:* Regional Office	International Application: Receiving Office
item (1)	27 April 1998 (27.04.98)	60/083,133	US		
item (2)					
item (3)					

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

**Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /US

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the

request	:	5
description (excluding sequence listing part)	:	16
claims	:	4
abstract	:	2
drawings	:	8
sequence listing part of description	:	0
Total number of sheets	:	35

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: **CHECK**

Figure of the drawings which should accompany the abstract: **FIG. 1**

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Michael I. Falkoff

Dated: 26 April 1999

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	☐ received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau: